Cover Page for Statistical Analysis Plan

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16.1.9 Documentation of statistical methods

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Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

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Statistical Analysis Plan

Trial ID: NN9068-4184

DUAL™ II Japan - Insulin degludec/liraglutide (IDegLira) vs. insulin degludec (IDeg) therapy

A clinical trial comparing efficacy and safety of insulin degludec/liraglutide (IDegLira) versus insulin degludec (IDeg) therapy in subjects with type 2 diabetes mellitus

Author:

[redacted]

Biostatistics IDegLira

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
BG	blood glucose
CAS	completer analysis set
CTR	clinical trial report
ECG	electrocardiogram
ET	End of treatment
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPG	fasting plasma glucose
$HbA1_c$	glycosylated haemoglobin
HDL	high density lipoprotein
IDegLira	insulin degludec/liraglutide
IDeg	insulin degludec
ITT	intention-to-treat
LDL	low density lipoprotein
LLOQ	lower limit of quantification
LOCF	Last Observation Carried Forward
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SMPG	self-measured plasma glucose
T2DM	type 2 diabetes mellitus
TEAEs	treatment emergent adverse events
UTN	Universal Trial Number
VLDL	very low density lipoprotein

1 Introduction

1.1 Trial information

This phase 3 trial is a 26-week randomised, parallel two-arm, double-blinded, multi-centre, treat-to-target trial in Japanese subjects with T2DM inadequately controlled with basal insulin or pre-mix/combination insulin, combined with metformin with or without one of the following OADs: SU, glinides, α-GI, SGLT2i or TZD, hereafter collectively referred to as other OADs. The trial is comparing efficacy and safety of insulin degludec/liraglutide (IDegLira) versus insulin degludec (IDeg) both in combination with Metformin. For further details please see the protocol.

1.2 Scope of the statistical analysis plan

This Statistical Analysis Plan (SAP) is based on Final Protocol version 4.0 (15-Dec-2016).

The scope of this SAP is to specify the statistical analysis for change from baseline in body weight after 26 weeks of treatment and add sensitivity analysis for change from baseline in $HbA1_c$ after 26 weeks of treatment due to protocol amendment 2 during recruitment of subjects. Furthermore, some errors have been corrected. For further details on the changes see section 3.

2 Statistical considerations

Novo Nordisk will analyse and report data from all sites together.

All analyses of efficacy and safety endpoints will be based on the full analysis set (FAS). All efficacy endpoints will be summarised using the FAS and safety endpoints will be summarised using the safety analysis set (SAS).

The impact of protocol deviations and outliers may be investigated further in the sensitivity analyses if deemed relevant.

Unless otherwise specified, all continuous measurements will be summarised descriptively at each visit by treatment using observed data. After 26 weeks of treatment, descriptive statistics will be presented based both on observed and last observation carried forward (LOCF) imputed data. Endpoints that are analysed untransformed and endpoints that are not formally analysed are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum values. Endpoints that are analysed log-transformed are supplemented with the geometric mean and coefficient of variation (CV).

For measurements over time, mean values will be plotted to explore the trajectory over time. LOCF imputed data will be used as the basis for plotting data, if not otherwise specified. For endpoints that are analysed log-transformed, the geometric mean values will be plotted.

A standard analysis of covariance (ANCOVA) model will be applied for the continuous primary and secondary endpoints. The model includes treatment, pre-trial anti-diabetic treatment (metformin + basal insulin, metformin + one other OAD + basal insulin, metformin + pre-mix/combination insulin, metformin + one other OAD + pre-mix/combination insulin) as fixed factors and the corresponding baseline value as covariate. In the following, this model will be referred to as the standard ANCOVA model.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (Least Square Means [LSMeans]) for absolute values and change from baseline. In addition, estimated mean treatment difference (or ratio) will be presented together with the two-sided 95% confidence interval and corresponding two-sided p-value.

Handling of missing data

The expected percentage of missing data is around 15%. In accordance with industry guidance endpoints will be assessed at frequent visits. If an assessment was made both at screening (V1) and randomisation (V2), and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value was used as the baseline value.

Missing values (including intermittent missing values) will be imputed using the LOCF method. Subjects without data after randomisation will be included by carrying forward their baseline value. LOCF has been a standard approach in diabetes trials for many years, and was used as the primary analysis in both IDegLira and IDeg phase 3 trials. LOCF is considered to be an appropriate method in the context of treat-to-target trials, where subjects after withdrawal typically continue their therapy using commercially available insulin. In previous treat-to-target trials with IDegLira and IDeg, LOCF has generally provided similar results to alternative methods applied to handle missing data, such as repeated measures models and completer analyses. In this trial, similar sensitivity analyses will be made to examine the robustness of the LOCF method

2.1 Sample size calculation

Sample size calculations are described in the protocol section 17.1 and will not further be described here.

2.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance[1]:

- **Full Analysis Set (FAS)**: includes all randomised subjects. In exceptional cases, subjects may be eliminated from the full analysis set. In such cases the elimination will be justified and

documented. The statistical evaluation of the FAS will follow the intention-to-treat principle and subjects will contribute to the evaluation "as randomised"

- **Safety Analysis Set (SAS)**: includes all subjects receiving at least one dose of the investigational product or comparator. Subjects in the safety set will contribute to the evaluation "as treated"

Randomised subjects who are lost to follow-up and where no exposure information of the investigational product or comparators is available after randomisation will be handled as unexposed.

Before data are released for statistical analysis, a review of all data will take place to identify protocol deviations that could potentially affect the results. Any decision to exclude any subject or observation from the statistical analysis is the joint responsibility of the members of the sponsor study group. The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

2.3 Primary endpoint

The primary endpoint is defined as change from baseline in HbA_{1c} after 26 weeks of treatment.

The change from baseline in HbA_{1c} after 26 weeks of treatment will be analysed using an ANCOVA model with treatment, pre-trial anti-diabetic treatment (metformin + basal insulin, metformin + one other OAD + basal insulin, metformin + pre-mix/combination insulin, metformin + one other OAD + pre-mix/combination insulin) as fixed factors and baseline HbA_{1c} as covariate. Missing values after 26 weeks of treatment will be imputed applying LOCF using HbA_{1c} values at and after baseline.

Superiority of IDegLira vs. IDeg will be considered as confirmed if the 95% confidence interval for the mean treatment difference for change from baseline in HbA_{1c} lies entirely below 0.0%; equivalent to a one-sided test with significance level of 2.5%. Conclusion of superiority will be based on FAS.

2.3.1 Sensitivity analysis

Sensitivity analysis will be performed on FAS using the mixed model for repeated measurement (MMRM) to evaluate the robustness of using LOCF. All HbA_{1c} values available post baseline at scheduled measurement times will be analysed in a linear mixed normal model using an unstructured residual covariance matrix for HbA_{1c} measurements within the same subject. The model will include treatment, visit and pre-trial anti-diabetic treatment as fixed factors and baseline HbA_{1c} as covariate. Interactions between visit and all factors and between visit and baseline HbA_{1c} are also included in the model.

Further, a pattern mixture model approach, mimicking an intention-to-treat scenario will be applied. The imputation in the IDegLira arm will be based on IDeg values. It will be done as follows:

- In the first step intermittent missing values are imputed using a Markov Chain Monte Carlo method, in order to obtain a monotone missing data pattern. This imputation is done for each treatment group separately and 1000 copies of the dataset will be generated.
- In the second step, for each of the 1000 copies of the dataset, an analysis of variance model with treatment and pre-trial anti-diabetic treatment as fixed factors, and baseline HbA_{1c} as covariates is fitted to the change in HbA_{1c} from baseline to 4 weeks (V10) for the comparator group only. The estimated parameters, and their variances, from this model are used to impute missing values at 4 weeks for subjects in comparator and IDegLira treatment groups, based on pre-trial anti-diabetic treatment and HbA_{1c} at baseline.
- In the third step, for each of the 1000 copies of the dataset, missing HbA_{1c} values at 8 weeks (V14) are imputed in the same way as for 4 weeks. Now the imputations are based on an analysis of variance model with the same factors and the HbA_{1c} values at baseline and 4 weeks as covariates, fitted to the comparator group.
- This stepwise procedure is then repeated sequentially over the available planned visits, adding one visit in each step until the last planned visit at 26 weeks (V32)
- For each of the complete data sets, the change from baseline to 26 weeks is analysed using an analysis of variance model with treatment and pre-trial anti-diabetic treatment as fixed factors and baseline HbA_{1c} value as a covariate.

The estimates and standard deviations for data sets are pooled to one estimate and associated standard deviation using Rubin's rule[3]. From these pooled estimates the confidence interval for the treatment differences and the associated p-value are calculated.

The results of the sensitivity analyses will be compared to the result of the standard ANCOVA method using LOCF for imputation of missing data. Any marked difference between the MMRM, the pattern mixture approach and ANCOVA LOCF approach regarding the estimated treatment difference will be commented upon in the clinical trial report.

Additional sensitivity analysis will be performed comparing the treatment difference in subjects recruited by one set of criteria compared to ones recruited with updated set of criteria, in order to evaluate the impact of protocol amendment 2 (08-Sep-2016) implemented during recruitment of subjects.

2.4 Secondary endpoints

2.4.1 Supportive secondary endpoints

2.4.1.1 Efficacy endpoints

Insulin dose after 26 weeks of treatment
The actual daily dose after 26 weeks of treatment will be analysed using the standard ANCOVA model including treatment and pre-trial anti-diabetic treatment as fixed factors and baseline HbA_{1c} value and baseline insulin dose as covariates.

Body weight
The change from baseline in body weight after 26 weeks of treatment will be analysed using the standard ANCOVA model with treatment and pre-trial anti-diabetic treatment as fixed factors and baseline body weight as covariate. Missing values after 26 weeks of treatment will be imputed applying LOCF using body weight values at and after baseline.

Responder after 26 weeks of treatment
Two dichotomous endpoints (responder/non-responder) will be defined based on whether a subject has met a specific target level after 26 weeks of treatment:

- $HbA_{1c} < 7.0\%$
- $HbA_{1c} \leq 6.5\%$

Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment and pre-trial anti-diabetic treatment as fixed factors and baseline HbA_{1c} values as a covariate.

HbA_{1c} responder endpoints without weight gain after 26 weeks of treatment
Responder for HbA_{1c} without weight gain after 26 weeks of treatment will be defined as HbA_{1c} $<7.0\%$ or $\leq 6.5\%$ at ET and change from baseline in body weight bellow or equal to zero. Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment and pre-trial anti-diabetic treatment as fixed factors and baseline HbA_{1c} and baseline body weight values as covariates.

HbA_{1c} responder endpoints without hypoglycaemic episodes
Responder for HbA_{1c} without hypoglycaemic episodes after 26 weeks of treatment will be defined as $HbA_{1c} < 7.0\%$ or $\leq 6.5\%$ at ET and without treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment. Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment and pre-trial anti-diabetic treatment as fixed factors and baseline HbA_{1c} values as a covariate.

HbA_{1c} responder endpoints without hypoglycaemic episodes and weight gain
Responder for HbA_{1c} without hypoglycaemic episodes and weight gain after 26 weeks of treatment will be defined as $HbA_{1c} < 7.0\%$ or $\leq 6.5\%$ at ET, without treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment, and change from baseline in body weight bellow or equal to zero. Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment and pre-trial anti-diabetic treatment as fixed factors and baseline HbA_{1c} and body weight values as covariates.

Fasting plasma glucose (FPG)
Change from baseline in FPG after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Waist circumference
Change from baseline in waist circumference after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Blood pressure (systolic and diastolic)
Change from baseline in blood pressure after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Self-measured blood glucose (SMBG) 9-point profile
The following six endpoints from the 9-point profile will be defined:

- 9-point profile (individual SMBG values) [One endpoint]
- Mean of the 9-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time [One endpoint]
- Prandial plasma glucose increments (from before meal to 90 min after for breakfast, lunch and dinner). The mean increment over all meals will be derived as the mean of all available meal increments [Four endpoints]

A linear mixed effect model will be fitted to the 9-point SMBG profile data. The model will include treatment, pre-trial anti-diabetic treatment, time, the interaction between treatment and time and the interaction between pre-trial anti-diabetic treatment and time as fixed factors and subject as random effect. From the model mean profile by treatment and relevant treatment differences will be estimated and explored.

Change from baseline after 26 weeks of treatment in mean of the 9-point profile and post-prandial increment endpoints will be analysed separately using the standard ANCOVA model.

Lipids
Total cholesterol, low density lipoprotein cholesterol (LDL cholesterol), high density lipoprotein cholesterol (HDL cholesterol), very low density lipoprotein cholesterol (VLDL cholesterol),

triglycerides, and free fatty acids after 26 weeks of treatment will be analysed separately by using the standard ANCOVA model. In these statistical analyses the endpoint will be log-transformed and so will the baseline covariate.

2.4.1.2 Safety endpoints

Adverse events

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities.

A TEAE is defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. If the event has onset date before the first day of exposure on randomised treatment and increases in severity during the treatment period and until 7 days after the last drug date, then this event should also be considered as a TEAE. Here the first day of IMP administration is defined as the first day of exposure to randomised treatment.

TEAEs are summarised descriptively, whereas non-TEAEs are presented in listings. TEAE data will be displayed in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years of exposure (R).

Summaries of TEAEs and of serious TEAEs will be presented as an overview including all AEs, serious AEs, number of deaths, AEs by severity, AEs by relation to treatment and AEs of special interest including AEs leading to withdrawal.

Furthermore summary tables based on system organ class and preferred terms are made for:

- All TEAEs
- Serious TEAEs
- Possibly or probably related TEAEs
- Severe, moderate and mild TEAEs
- TEAEs reported by safety areas of interest
- TEAEs with preferred term that are experienced by at least 5% of the subjects in any treatment arm or by at least 5% of all subjects

A listing for non-TEAEs with onset date before the first day of exposure to randomised treatment will be presented. A listing will also be presented for non-TEAEs collected after the treatment emergent period according to the definition of TEAE.

Hypoglycaemic events

Data on treatment emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R).

Separate summaries are made for severe or BG confirmed hypoglycaemic episodes, severe or BG confirmed symptomatic hypoglycaemic episodes, , nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes and the ADA classification of hypoglycaemia.

The number of hypoglycaemic episodes during 26 weeks of treatment will be analysed separately for each endpoint using a negative binominal regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment and pre-trial anti-diabetic treatment as fixed factor.

Clinical evaluations (physical examination, eye examination and ECG)
Eye examination (fundoscopy/fundus photography) and ECG findings will be summarised descriptively, including:

- summaries for each visit
- shift table from baseline to after 26 weeks of treatment

Any findings in the physical examination evaluation at screening will be presented as listings. Any clinically significant deterioration of a pre-existing condition after the screening visit, as well as any new clinically significant findings will be recorded as AEs.

Pulse
Change from baseline in pulse after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Laboratory assessments
All laboratory parameters will be summarised descriptively.

The following tables will be presented based on both observed and LOCF imputed data:

- Shift tables from baseline to after 26 weeks of treatment
- Proportion of subjects with measurements outside reference range by treatment and week

Laboratory values will be presented graphically as box plots by treatment and week. For each laboratory parameter, individual values outside the reference ranges (abnormal values) will be listed.

Calcitonin
The purpose of the calcitonin analysis is to evaluate longitudinal changes in calcitonin, with main focus on subjects who develop persistently high levels of calcitonin during the trial.

Calcitonin will be displayed in terms of the number of subjects (N), the percentage of subjects (%) and the incidence rate per 100 years of exposure (R).

The following criteria are defined for tabulations:

Persistent (all post baseline measurements)

- From < UNR to persistently ≥ UNR
- From < UNR to persistently ≥ 1.5 UNR
- From < UNR to persistently ≥ 20 ng/L
- From < UNR to persistently ≥ 50 ng/L
- From < 20 ng/L to persistently ≥ 20 ng/L
- From < 50 ng/L to persistently ≥ 50 ng/L

Incidental (at least one post baseline measurements)

- From < UNR to ≥ UNR
- From < UNR to ≥ 1.5 UNR
- From < UNR to ≥ 20 ng/L
- From < UNR to ≥ 50 ng/L
- From < 20 ng/L to ≥ 20 ng/L
- From < 50 ng/L to ≥ 50 ng/L

The distribution of all calcitonin measurements across treatment groups and time will be shown with box plots and corresponding cumulative plots for actual levels of calcitonin and change from baseline. The plots will be presented by treatment group (using ET measurement - LOCF) and within treatment group by week. Plots will be done by each gender, separately.

Summaries tables of calcitonin continuous measurements, will include number and percentage of observations < and ≥ lower limit of quantification (LLOQ), minimum, Q25, median, Q75 and maximum. Summaries will be presented for all subjects and by gender.

Longitudinal changes for subjects with calcitonin levels ≥ 20 ng/L will be plotted (longitudinal plots). The plots will be done by treatment and gender. They will be done for subjects in the persistent and incidental categories, separately.

A listing of subjects with at least one post baseline value ≥ 20 ng/L will be done. The listing will include age, gender, calcitonin measurements over time and AE history (including preferred term, onset and stop dates).

2.4.2 Patient reported outcomes

The following questionnaires will be used to compare PROs between treatments:

- DTR-QOL questionnaire
- EQ-5D-5L questionnaire

The questionnaires will be summarised descriptively by visit and treatment.

For the DTR-QOL questionnaire change from baseline in the following scores will be analysed separately using the standard ANCOVA:

- Domain QOL scores
    - Burden on social activities and daily activities
    - Anxiety and dissatisfaction with treatment
    - Hypoglycemia
    - Satisfaction with treatment
- Total QOL score

For the EQ-5D-5L questionnaire change from baseline in QOL and VAS scores will analysed separately using the standard ANCOVA.

Quality Adjusted Life Years will be evaluated in a separate report by the Novo Nordisk Health Economics and Outcomes Research department.

3 Changes to the statistical analyses planned in the protocol

Corrections have been made to the supportive secondary endpoints. The description of analysis of change from baseline in body weight after 26 weeks of treatment has accidently been left out of protocol, however listed in the endpoint section of the protocol.

Additional sensitivity analysis for change from baseline in $HbA1_c$ has been added to further evaluate the impact of protocol amendment 2 (08-Sep-2016) implemented during recruitment of subjects for this trial. In this amendment inclusion and exclusion criteria was changed, therefore a sensitivity analysis comparing treatment difference in subjects recruited by one set of criteria will be compared to ones recruited with updated set of criteria.

Box plots have replaced the planned histograms for calcitonin.

4 References

1. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials E9. International Conference on Harmonisation E9 Expert Working Group. September 1998.

2. O'Kelly M, Ratitch B. Clinical trials with missing data : a guide for practitioners. 2014.
3. Little RJA, Rubin D.B. Statistical analysis with missing data. New York: John Wiley & Sons, 1987.